PATENT
Attorney Docket No. 01975.0025-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Rudi BRANDS	)	Group Art Unit: 1651
	)	
Application No.: 09/582,342	)	Examiner: A. Ford
	)	
Filing Date: September 18, 2000	)	Confirmation No. 8325
	)	
For: PREPARATION OF CELLS FOR PRODUCTION OF BIOLOGICALS	)	**VIA EFS-WEB**

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REPLY BRIEF UNDER 37 C.F.R. § 41.41

Pursuant to 37 C.F.R. § 41.41, Appellants present this Reply to the Examiner's Answer dated June 10, 2009 ("Answer"). This Reply is timely filed within two-months of the June 10, 2009, mailing date of the Answer, i.e., August 10, 2009.

I. STATUS OF REJECTIONS

Claims 39-44 are pending. Claims 1-38 are canceled. Claims 39-44 stand rejected and are appealed. No claim has been allowed.

II. RESPONSE TO EXAMINER'S ARGUMENTS IN ANSWER

Claims 39-44 remain rejected under 35 U.S.C. § 103 over BRYAN GRIFFITHS & DENIS LOOBY, *Scale-Up of Suspension and Anchorage-Dependent Animal Cells, in* 75 METHODS IN MOLECULAR BIOLOGY: BASIC CELL CULTURE PROTOCOLS 59, 59-75 (Jeffrey W. Pollard & John M. Walker eds., 2d ed. 1997) ("Griffiths") in view of "Friendship Cake/Bread History" available at http://recipecircus.com and "Amish Friendship Bread" available at http://en.wikipedia.org. *See* Answer at p. 4. Appellants maintain their position that the Examiner has failed to establish that these claims are unpatentable over the cited references for the reasons of record and the additional reasons discussed below.

A. The Examiner Has Failed to Establish a *Prima Facie* Case of Obviousness over the Cited References

1. The Examiner has Failed to Establish that the Cited References Teach or Suggest All the Claim Limitations

In the Appeal Brief filed March 6, 2009 ("Appeal Brief"), Appellants argued that Griffiths does not disclose "splitting" the cells in the manner claimed. *See* Appeal Brief at p. 11. In response, the Examiner points out that Griffiths recite the cells, once detached via enzymatic action, are "'harvested, diluted in fresh medium and serum, and **passaged on**' (see Griffths et al., Pg. 67, step #6)." Examiner's Answer at p. 8 (emphasis added). The Examiner explains that "passaging of cells" as described in

Griffiths is a term of art which involves dilution in fresh media and subsequent seeding of a portion of the diluted cell culture *See id.* The Examiner asserts that "[s]plitting of the cell culture is an inherent aspect of passaging, as it is required to reduce the cell concentration in order to maintain cell viability." *See id* Appellants respectfully disagree.

A "passage step" is defined in Appellants' specification as:

> . . . a sequence of activities in the propagation and production of cells comprising at least the transfer of a suitable amount of cells and of a suitable amount of culturing medium into a production vessel, the incubation of the vessel at conditions suitable for the growing a propagation of the cells during a time sufficient for effective growing and propagation of the cells during a time sufficient for effective growing and propagation of the cells.

Appellants' specification at p. 3, lines 12-16. Based on this definition it is clear that "passaging of cells" involves transferring a number of cells from an existing vessel into a new vessel and is not the same as splitting the cells into two parts as in independent claim 39.

Griffiths describes two approaches to scale-up: "The first [approach] is volumetric -- a simple increase in volume while retaining the same cell density or process intensity. *See* Griffiths at p. 60, lines 3-4. The second method [of scale-up] is to increase the cell density/unit vol 10-100-fold by means of medium perfusion techniques." *See id.* at lines 4-6. Griffiths further teaches that scaling up "can be achieved by increasing the culture volume, and increasing the microcarrier concentration from the suggested 3-15 g/L." *See id.* at p. 71, lines 15-17. Thus, the scale-up approaches described in Griffiths teach that the cell culture as a whole, not

merely a portion of the cells, is transferred (or passaged) to a larger scale cultivation device. Moreover, while Griffiths may teach passaging of cells, the passaging of cells in Griffiths is not the same as splitting the cells into two parts where "a) a first part of the cells of the preproduction batch is used for the preparation of at least one production batch, and b) the remaining part of the cells of the preproduction batch is used as a seed for the preparation of at least one subsequent preproduction batch," as defined in independent claim 39. Accordingly, Appellants maintain that Griffiths fails to teach or suggest all the claim limitations.

2. The Examiner failed to Meet her Burden under the TSM rationale

In the Appeal Brief, Appellants argued that:

> Applying the Graham factors, and considering the level of ordinary skill in the area of cell culture protocols, one would not conclude that this level includes the skill of a baker. Therefore, there is no reason why one of ordinary skill in that particular art would consider applying techniques used in making bread to a process for preparing cells for the production of a biological, for example, a virus.

Appeal Brief at p. 12.

In response, the Examiner asserts that:

> [S]ourdough starter is actually a cell culture, it is an active yeast culture, and therefore is relevant to the art of cell culture in at least as far as it pertains to methods of propagating cell culture. Furthermore, it is submitted that the discussion of sourdough friendship bread was only relied upon to show the extreme commonness of the idea of "repeated discontinuous" processes of culture. Still further, it has been held that '[W]hen a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.' KSR

> International Co. v. Teleflex, Inc., 82 USPQ2d 1385 (U.S. 2007) at 1396. Thus, even if one were to interpret propagation of sourdough starter culture as being non-analogous to cell culture, modifications and variations to improve methods can be imported across different fields of art.

Id. Appellants respectfully disagree.

While modifications and variations to improve methods can be imported across different fields of art, Appellants point out that here, there is no reason that one of ordinary skill in the art would import the techniques used in making bread, even if cell cultures are employed, for use in a method for the preparation of cells for use in the production of a biological.

For one thing, the challenges associated with scaling up anchorage-dependent cells are very different from the challenges associated with bread making. The use of a repeated discontinuous splitting process of anchorage-dependent cells for production of a biological would require the use of new microcarriers as well as the re-use of microcarriers used in the pre-culture. Yet, one skilled in the art would have serious doubts about whether microcarriers could be re-used, and may even regard their re-use as impossible. In addition, the use of new microcarriers and the re-use of microcarriers would result in increased heterogeneity of the culture, leading to homogeneity problems. There is no reason why one skilled in the area of cell cultures would consider applying techniques used in making bread to solve these problems. Moreover, given that the process of making bread is completely unrelated to the scale-up procedures of anchoarge-dependent cells, there is no way one of ordinary skill in the art would have been able to predict the results of using anchorage-dependent cells in a repeatable

discontinuous splitting process for the production of a biological with any reasonable expectation of success.

In view of the foregoing, Appellants maintain that the Examiner has failed to meet her burden under the TSM rationale.

3. The Art Teaches Away from The Claimed Invention

In the Appeal Brief, Appellants detailed the technical difficulties associated with scaling up anchorage-dependent cells for production of biologicals. Thus, Appellants argued that the art teaches away from the claimed invention. In response, the Examiner notes that Griffiths recognizes the technical difficulties associated with scaling-up of anchorage-dependent cell cultures. The Examiner asserts that, "Griffiths et al is specifically directed to methods to overcome these technical difficulties, thus the prior art does not teach away, but specifically teaches known methods of addressing the technical difficulties." Office Action at p. 9. Appellants respectfully disagree.

Griffiths generally discusses the scale up of suspension and anchorage-dependent cells. While Griffiths may touch on the difficulties associated with scaling up anchorage-dependent cells, there is nothing in Griffiths that teaches or suggests using a repeated discontinuous process (of scaling up) for addressing or solving these difficulties. In fact, because of the difficulties associated with scaling up anchorage-dependent cells, other references in the pertinent art teach away from scale-up of anchorage-dependent cells for use in the production of a biological. Indeed, Appellants pointed out one such reference, WO 97/37000 to Gröner et al. ("Gröner"), on page 13 of their Appeal Brief.

Griffiths describes two approaches to scale-up: "The first [approach] is volumetric -- a simple increase in volume while retaining the same cell density or process intensity. *See* Griffiths at p. 60, lines 3-4. The second method is to increase the cell density/unit vol 10-100-fold by means of medium perfusion techniques." *See id.* at 4-6. Griffiths further teaches that scaling up "can be achieved by increasing the culture volume, and increasing the microcarrier concentration from the suggested 3-15 g/L." *See id.* at p. 71, lines 15-17. Thus, the scale-up approaches described in Griffiths teach that the cell culture as a whole, not merely a portion of the cells, is transferred (or passaged) to a larger scale cultivation device.

U.S. Patent No. 4,664,912 to Wiktor et al. ("Wiktor"), which also deals with scaling up of anchorage-dependent cells for use in the production of biologicals, teaches a scale-up procedure that is similar to the procedure disclosed in Griffiths. As described in the specification at page 1, Wiktor describes a method for preparing a large volume of anchorage-dependent cells beginning with a seed population. Specifically, Wiktor teaches that the scaling-up of anchorage-dependent cells requires passage of the whole set of microcarrier balls for each scaling-up round. *See* Wiktor at col. 3, lines 18-28 and col. 5, lines 14-52. Wiktor teaches that one may successively pass all of the progeny into successively larger bioreactors until an optimum volume is achieved. *See* Wiktor at col. 2, lines 59-67. It is only after several generations of this continuous process that the cells are harvested for their intended use. *See id.*

The teachings of Wiktor are consistent with the teachings of Griffiths. Thus, Wiktor substantiates what is already demonstrated by Griffiths, namely that, contrary to

the Examiner's assertions[1], the "common sense" of scaling-up anchorage-dependent cells involves passaging the whole batch of cells. This is inconsistent with the repeated discontinuous process claimed in independent claim 39. Hence, Griffiths, Gröner (which is discussed in the Appeal Brief), and Wiktor, which are all more relevant to the claimed area of endeavor than the "Friendship Cake/Bread History" and "Amish Bread" articles cited by the Examiner, in no way teach or suggest that a repeated discontinuous (splitting) process as defined in independent claim 39 could or would be applied to anchorage-dependent cells. In fact, these references teach away from such a process. Accordingly, one skilled in the art would be unlikely to use a repeated discontinuous splitting process when using anchorage-dependent cells for the production of a biological.

III. CONCLUSION

For the reasons given above, Appellants maintain that claims 39-44 are allowable and reversal of the Examiner's rejection is respectfully requested.

[1] The Examiner's assertions are based on art that is completely unrelated to a method for the preparation of cells for the use in the production of a biological.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Reply Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: August 7, 2009

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